

Remarks

I. Status of the Application and Claims

As originally filed, the present application had a total of 4 claims. These were cancelled in a Preliminary Amendment and new claims 5-24 were added. No claims were cancelled or added herein.

II. The Amendments

Claim 5 was amended to eliminate two words, "derivatives" and "general," that the Examiner found to be objectionable. It was also amended to indicate that crystallization is induced during the addition of oxidizing agent to the reaction. Support for various measures for inducing crystallization may be found on page 5 of the application, lines 16-29.

Claims 6, 10 and 14 were amended to specify particular hydroxyproline starting compounds. Support for these amendments may be found on page 7 of the application, lines 13-26.

Claims 7, 11 and 15 were amended to recite 30°C rather than 20°C. Support for these amendments may be found in pre-amendment claims 6, 10 and 14.

None of the amendments made herein add new matter to the application and there entry is therefore respectfully requested.

III. Claim Objections

On page 3 of the Office Action, the Examiner objects to claims as containing non-elected species, apparently because the Examiner has alleged that the claims are obvious. According to MPEP §803.02, when this occurs:

the provisional election will be given effect and examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.

Thus, Applicants believe that the proper procedure under these circumstances is for the Markush claim (*i.e.*, claim 5 in the present case) to continue in Examination and for the Examiner to withdraw any non-Markush claims that are directed to particular species. Since

there are no claims directed solely to non-elected species that are pending, Applicants do not believe that any need to be withdrawn even though they modify claim 1 and this is still in a Markush format. Thus, Applicants do not believe that amendments to eliminate subject matter from dependent claims need to be made at present.

The Rejections

I. Rejection of Claims Under 35 USC § 112, Second Paragraph

On pages 3 and 4 of the Office Action, the Examiner rejects all pending claims under 35 USC §112, second paragraph, based upon the allegation that the terms "derivatives" and "general" render the claims indefinite.

In response, Applicants have amended claims to eliminate both of the terms that the Examiner alleges are problematic. In light of these amendments, Applicants respectfully submit that the present rejection has been obviated.

II. Rejection of Claims Under 35 USC § 103

On pages 4-5 of the Office Action, the Examiner rejects all pending claims as being obvious over Dormoy, *et al.* (*Synthesis*, pg. 81-86 (1996)), in view of Carlsen, *et al.*, (*J. Org. Chem.* 46:3936-3938 (1981)) and Riley, *et al.* (*J. Chem. Soc., Chem. Commun.*, 1530-1532 (1983)) and further in view of Narukawa, *et al.* (*Tetrahedron* 53:539-556 (1997)). The Examiner alleges that Dormoy teaches the conversion of hydroxyprolines to ketoprolines using a ruthenium catalyst in a biphasic organic solvent system. Carlsen and Riley are both cited as teaching ruthenium catalyzed oxidations in solvent systems containing water and Narukawa is cited as teaching that t-boc protected oxo-proline compounds are not very soluble in water. The Examiner argues that one of skill in the art would be motivated to use the one phase aqueous system of Riley with the reaction of Dormoy in order to simplify the procedure and use less toxic materials. The low solubility of compounds in water would allegedly suggest to one of skill in the art that precipitations may be induced in aqueous media to stabilize compounds.

Applicants respectfully traverse this rejection.

As discussed on pages 4 and 5 of the application, the main problem with ketoproline compounds of the type made by the claimed process is that they are unstable, *i.e.*, they readily undergo further, unwanted, transformations. In order to minimize this, two phase systems were developed in which the compounds undergoing oxidation and the oxidized product are in the organic phase and the oxidizing agents are located in the aqueous phase. As a result, oxidations only occur at the interface. This is the system that is described in the Narukawa reference. Although this system may be effective at protecting ketoprolines, it is also inefficient and cumbersome.

The presently claimed process is carried out in a one phase solvent system and relies on rapid precipitation to protect the ketoproline products made. As discussed on page 4 of the application, lines 8-15, the process requires that precipitations occur rapidly after reaction, preferably immediately. This is why the present claims require that the ketoproline product be induced to crystallize at the same time that oxidizing agent is being added to the system. It is not just the precipitation that is important, but also the timing of the precipitation.

The reference by Dormoy discloses a two phase system in which a ketoproline is formed as an intermediate. It should be noted that rapid precipitation is not used to protect the ketoproline from further transformations. In fact, the ketoproline is purified by extraction and not precipitated at all. Carlsen and Narukawa both use two phase aqueous/organic solvent systems and neither suggests that rapid precipitation of ketoprolines may be employed to stabilize them.

Although Riley uses a one phase system, ketoprolines are not among the oxidation products considered and it is not clear that stability problems of the same degree exist for the compounds studied. Moreover, the products in Riley were analyzed directly in solution and not precipitated or otherwise purified (see footnote on page 1531).

Overall, Applicants submit that a main element required by the pending claims, stabilization of ketoproline products by inducing precipitation at the same time that oxidizing agent is added, is not suggested by any of the references cited and, even if the references are combined, this element is totally lacking.

Although the Examiner alleges that Narukawa teaches that ketoproline are not very soluble in water, Applicants have been unable to find such a teaching in the reference. Even if present, it is not clear how this would serve as a motivation to actively induce precipitation while adding oxidizing agent to protect ketoproline from unwanted reactions.

Conclusion

In light of the discussion above, Applicants respectfully submit that all of the Examiner's rejections have been overcome. It is therefore requested that these rejections be withdrawn and that the claims presently pending in the application be allowed.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (240)683-6165.

Respectfully submitted,
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